

## PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference  
see form PCT/ISA/220FOR FURTHER ACTION  
See paragraph 2 belowInternational application No.  
PCT/GB2004/002678International filing date (day/month/year)  
22.06.2004Priority date (day/month/year)  
26.06.2003International Patent Classification (IPC) or both national classification and IPC  
C07K508Applicant  
PEPHARM B.B. LIMITED

## 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

## 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 65.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

## 3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/GB2004/002678**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITYInternational application No.  
PCT/GB2004/002678

## Box No. II Priority

1. ☒ The following document has not been furnished:☒ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITYInternational application No.  
PCT/GB2004/002678**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,  
☒ claims Nos. 1,2,4-10,25,26,28,29 (all in part)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1,2,4-10,25,26,28,29 (all in part)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- |                            |  |
|----------------------------|--|
| the written form           | <input type="checkbox"/> has not been furnished            |
|                            | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished            |
|                            | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☒ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/GB2004/002678**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1. Statement**

Novelty (N)	Yes: Claims	5,8,10-18,20-24,27
	No: Claims	1-4, 6,7,9,19,25,26,28,29
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-29
Industrial applicability (IA)	Yes: Claims	1-13,18-20 and 25-29
	No: Claims	14-17, 21-24 see SepSheet

**2. Citations and explanations**

see separate sheet

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2004/002678

**Re Item III.**

Present claims 1, 2, 4-10, 25, 26, 28 and 29 relate to an extremely large number of possible compounds/methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the tripeptide Tyr-Ser-Val which was used in the experiments of the present application, to peptides with conservative amino acid substitutions and to peptides having less than 6 additional amino acids.

Moreover, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). Because of this, a meaningful search over the whole breadth of the claim(s) was impossible. Also for this reason, the search has been restricted to the peptides as indicated above.

According to Rule 66.1 (e) PCT claims relating to inventions in respect of which no International Search Report has been established need not be the subject of international preliminary examination which therefore was limited to the subject-matter that has been searched.

**Re Item V.****1. General Remarks****1.1 The following documents are referred to in this communication:**

- D1 : WO 03/006492 A (PEPHARM R & ; D LTD ; WONG WAI MING (CN); LIN GANG (CN); BALDOCK SHARON) 23 January 2003 (2003-01-23)  
D2 : WO 02/087507 A (SETH ARUN ; SUNNYBROOK & ; WOMEN S COLLEGE H (CA)) 7 November 2002 (2002-11-07)  
D3 : FURKA A ET AL: "STRING SYNTHESIS A SPATIALLY ADDRESSABLE SPLIT PROCEDURE" JOURNAL OF COMBINATORIAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 2, no. 3, 19

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2004/002678

May 2000 (2000-05-19), pages 220-223.

- 1.2 If not stated otherwise, the passages already cited in the International Search Report are referred to.

**2. Novelty (Article 33 (2) PCT)**

- 2.1 The subject-matter of claims 2, 4, 6, 9, 19, 26, 28 and 29 does not appear to be novel in view of D1. D1 discloses tripeptides Tyr-Ser-Leu and Tyr-Ser-Phe having the same activities as the tripeptide Tyr-Ser-Val of the present invention, namely modulation of the immune response (enhancement of the NK cell activity in mice with liver cancer and of the humoral immune response in mice with melanoma), reduction of the growth of liver cancer and melanoma, enhancement of T lymphocyte transformation etc. Said tripeptides of D1 are considered to represent peptides "consisting essentially of the tripeptide Tyrosyl-Seryl-Valine".
- 2.2 In addition, the subject-matter of claims 1, 2, 4, 6, 7, 9, 25, 26, 28 and 29 does not seem to be novel in view of D2. D2 describes breast cancer-associated (BCA) polypeptides as well as pharmaceutical compositions thereof for treating or preventing cancer, in particular breast cancer, and as food supplement. It discloses the peptide YSVT of BCA3 which is a fragment of its SH2 domain and which is considered to represent a peptide "consisting essentially of the tripeptide Tyrosyl-Seryl-Valine".
- 2.3 Moreover, the present application does not appear to meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1-4, 6 and 29 is not new in view of D3 which discloses already the tripeptide Tyr-Ser-Val.
- 2.4 In summary, claims 1-4, 6, 7, 9, 19, 25, 26, 28 and 29 do not seem to meet the requirements of Article 33(2)PCT.

**3. Inventive Step (Article 33 (3) PCT)**

- 3.1 Claims 5, 8 and 10, which refer to the L optical isomeric forms of the amino acids of the claimed peptides, do not appear to comprise any further technical features as compared to the disclosures of the prior art that could justify the acknowledgment of an inventive step. This is even more so, because the L isomeric form represents the form in which amino acids naturally occur in proteins.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2004/002678

3.2 The difference between the subject-matter of present claims 11-18, 20-24 and 27 and the subject-matter of D1 which is considered to represent the closest prior art, is the fact that the tripeptide of the present invention differs in the third amino acid position from the tripeptides YSL and YSP already disclosed by D1. The tripeptides of D1 display the same activities as the one claimed in the present application, i.e. modulation of the immune response, growth of different types of cancer etc., and D1 already discloses the medical use of said tripeptides.

Thus, the objective technical problem solved by the present invention appears to be the provision of a further tripeptide for the treatment of different types of cancer and as nutritional supplement.

The solution to this problem, namely the substitution of the amino acid Valine for Leucine and Phenylalanine, resp., appears to be obvious as it just represents a conservative replacement. In fact, this solution was already suggested by D1 which states that for peptides with non-polar or hydrophobic side chains it may be possible to substitute one side group for another without reducing the biological activity (see p. 56, lines 36-40).

3.3 Thus, the subject-matter of the present application does not appear to comprise an inventive step and does not seem to meet the requirements of Article 33(3) PCT.

**4. Further Remarks**

4.1 For the assessment of the present claims 14-17 and 21-24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.



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